Patent
Attorney's Docket No. 028723-020

#57
3 of 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Joe GRAY et al.

Application No.: 08/487,701

Filed: June 7, 1995

For: METHODS FOR STAINING TARGET CHROMOSOMAL DNA EMPLOYING NUCLEIC ACID PROBES

Group Art Unit: 1631

Examiner: A. Marschel

Appeal No.

BRIEF FOR APPELLANT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This appeal is from the decision of the Primary Examiner dated April 17, 2000 (Paper No. 54), finally rejecting claims 48, 49, 51-63, 65-69, 71-74, 76-86, 88-93, 95-97, and 102-104, which are reproduced as an Appendix to this brief.

A check covering the [ ] $155.00 (220) [X] $310.00 (120) Government fee and two extra copies of this brief are being filed herewith.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in triplicate.

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I. Real Party in Interest

The present application is assigned to The Regents of the University of California, and is licensed to Vysis, Inc.

II. Related Appeals and Interferences

The Appellants' legal representative, or assignee does not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

The status of the claims as set out in Paper No. 54 was and is as follows:

Allowed claims: 98-101 are allowed.

Claims 48, 49, 51-63, 65-69, 71-74, 76-86, 88, 90-93, 95, and 96 are rejected under 35 USC §112, first paragraph, as purportedly unsupported by an adequate written description in the specification.

Claim 74 is rejected under 35 USC §112, second paragraph, as purportedly indefinite.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are rejected under 35 USC §103(a) as purportedly obvious over U.S. Patent 4,710,465 to Weissman et al. (Exhibit A) in view of Lichter *et al.* (1988) *Proc. Natl. Acad. Sci. (USA)* 85:9664-9668.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claim 125 of copending application Serial No. 08/473,327.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 1, 48, and 50-58 of copending application Serial No. 08/477,316.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 1 and 48 of copending application Serial No. 08/487,387.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 62-65 and 125-148 of copending application Serial No. 08/478,740.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 18-33 of copending application Serial No. 08/472,312.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 131, 132, 144-147, and 150-153 of copending application Serial No. 08/487,974.

Claim 64 is objected to as dependent upon a rejected base claim, but is otherwise allowable.

IV. Status of Amendments

Applicants' most recent amendment, filed February 2, 2000 (Paper No. 53) has been entered. Entry of the attached amendment is respectfully requested. By that Amendment, claim 74 is amended to overcome the outstanding rejection under 35 USC §112, second paragraph. It is respectfully submitted that the attached amendment raises no new issues, and reduces the issues for appeal.

Also submitted herewith is a Petition to withdraw the Terminal Disclaimer filed in this case on August 6, 1999, over U.S. Patent No. 5,447,841.

V. Summary of the Invention

Applicants' invention is directed to a method of staining target chromosomal material using nucleic acid probes which are substantially complementary to unique nucleic acid segments.

VI. The Issues

Claims 48, 49, 51-63, 65-69, 71-74, 76-86, 88, 90-93, 95, and 96 are rejected under 35 USC §112, first paragraph, as purportedly unsupported by an adequate written description in the specification.

Claim 74 is rejected under 35 USC §112, second paragraph, as purportedly indefinite.

Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 are rejected under 35 USC §103(a) as purportedly obvious over U.S. Patent 4,710,465 to Weissman et al. (Exhibit A) in view of Lichter *et al.* (1988) *Proc. Natl. Acad. Sci. (USA)* 85:9664-9668.

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Claim 64 is objected to as dependent upon a rejected base claim, but is otherwise allowable.

VII. Grouping of Claims

For the purposes of the rejection of Claims 48, 49, 51-63, 65-69, 71-74, 76-86, 88, 90-93, 95, and 96 under 35 USC §112, first paragraph, as purportedly unsupported by an adequate written description in the specification, it is Applicants intention that the claims stand or fall together.

For the purposes of the rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under 35 USC §103(a) as purportedly obvious over U.S. Patent 4,710,465 to Weissman et al. (Exhibit A) in view of Lichter *et al.* (1988) *Proc. Natl. Acad. Sci. (USA)* 85:9664-9668, it is Applicants intention that the claims stand or fall together.

For the purposes of the provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as

purportedly obvious over claim 125 of copending application Serial No. 08/473,327, it is Applicants intention that the claims stand or fall together.

For the purposes of the provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 1, 48, and 50-58 of copending application Serial No. 08/477,316, it is Applicants intention that the claims stand or fall together.

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For the purposes of the provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 62-65 and 125-148 of copending application Serial No. 08/478,740, it is Applicants intention that the claims stand or fall together.

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VIII. Argument

1. The Rejection of Claims 48, 49, 51-63, 65-69, 71-74, 76-86, 88, 90-93, 95, and 96 Under 35 USC §112, first paragraph as purportedly unsupported by an adequate written description in the specification.

This rejection is based on the Examiner's assertion that the recitation in the present claims of probes with at least 40 kb of complexity introduces new matter into the claims. In particular, the Examiner argues, at page 4 of the Official Action mailed September 22, 1999 (Paper No. 52), that "all complexities for probes are described as being on the order of 50 kb or greater whereas the 40 kb size is only disclosed regarding a probe and not its

complexity." Applicants respectfully disagree, and maintain that the present specification provides ample explicit support for probes with a complexity of at least 40 kb.

At page 13, lines 6-7 of the specification, Applicants note that "prior to this invention, probes employed for *in situ* hybridization techniques had complexities below **40 kb,** and more typically on the order of a few kb." (Emphasis added). Applicants submit that this passage from the specification clearly distinguishes the present invention ("prior to this invention") from the prior art on the basis that, while the prior art methods of *in situ* hybridization required probes with complexities below 40 kb, the method of the presently claimed invention permits the use of probes with complexities of 40 kb or greater.

At page 38, lines 5-13, of the specification, Applicants reiterate that,

> The term "complexity" therefore refers to the complexity of the total probe no matter how many visually distinct loci are to be detected, that is, regardless of the distribution of the target sites over the genome.
>
> As indicated above, with current hybridization techniques it is possible to obtain a reliable, easily detectable signal with a probe of **about 40 kb** to about 100 kb (e.g. The probe insert capacity of one or a few cosmids) targeted to a compact point on the genome. Thus, for example, a complexity in the range of 100 kb now permits hybridization to both sides of a tumor-specific translocation.

(Emphasis added). Applicants directed the Examiner's attention to this passage in their most recent Reply, filed February 2, 2000. In response, at page 3 of the Official Action mailed April 17, 2000 (Paper No. 54) the Examiner argues that

> the page 38, lines 5-13, citation describes a probe of about 40 kb without defining this as complexity. It is noted that complexity and length are not identical concepts since the complexity is different in number due to accounting for repetitive sequences therein. Length, however, is length without such repetitive sequence compensation as to what is meant.

Applicants concede that probe complexity and probe length are not identical concepts. However, the Examiner has not explained why he chooses to interpret the reference at page 38 of the specification to "a probe of about 40 kb," in the midst of a discussion of probe complexity, as referring to probe length. Applicants respectfully submit that the only *reasonable* interpretation of the reference to 40 kb probes on page 38 is that it refers to probe complexity. In view of the foregoing, Applicants maintain that the pending claims fully comply with the requirements of 35 USC §112.

2. *The rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under 35 USC §103(a) as purportedly obvious over U.S. Patent 4,710,465 to Weissman et al. in view of Lichter et al. (1988) Proc. Natl. Acad. Sci. (USA) 85:9664-9668.*

This rejection is improper and unfounded. First, the present application claims benefit of U.S. Application Serial No. 06/ 937,793, filed December 4, 1986, which is a continuation-in-part of U.S. application Serial No. 06/819,314, filed January 16, 1986. Both of these applications were filed before the publication date of the Lichter et al. article, which is thus not properly cited as prior art against the present application.

More specifically, a method of staining target interphase chromosomal material as claimed is sufficiently described in the '314 application to satisfy the requirements of 35 U.S.C. §112, first paragraph. The function of the description requirement of §112 is to ensure that the applicant had possession, as of the filing date of his application, of the specific subject matter later claimed by him. It is required that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. *Behr v. Talbot,* 27 USPQ2d 1401, 1407 (BPAI 1992). *Ex Parte Raible,* 8 USPQ2d 1709, 1710 (PTO Bd App & Int 1988). *Ex Parte Harvey,* 3 USPQ2d 1626, 1627 (PTO Bd. App. & Int. 1987). This requirement is met for the claimed invention in the '314 application.

Applicants strenuously maintain that the reference to a "labeled nucleic acid probe having a complexity greater than about 40 kb" finds support and is sufficiently described in the '314 application to satisfy the requirements of 35 U.S.C. §112, first paragraph. In particular, the '314 application states at page 8, lines 6-12:

> The invention includes methods and compositions for staining chromosomes. In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of labeled nucleic acid fragments having substantial portions of substantially complementary base sequences to the chromosomal DNA for which specific staining is desired.

The '314 application further states:

> As discussed more fully below, preferably the heterogeneous mixtures are substantially free from so-called repetitive sequences, both the tandem variety and the interspersed variety (see Hood et al., Molecular Biology of Eucaryotic Cells (Benjamin/Cummings Publishing Company, Menlo Park, California, 1975) for an explanation of repetitive sequences).

Nucleic acid probes from which repeats have been removed and the use of blocking

nucleic acid are described at the very least at page 10, lines 1-10; page 19, line 14 to page 23, line 23. The staining of interphase chromosomal DNA is also described at the very least at page 10, lines 11-16; page 11, line 24 to page 12, line 2; and page 36, lines 6-9. furthermore, the '314 application states:

> In one preferred embodiment where the heterogeneous mixture is generated on a fragment-by-fragment basis, the chromosomal DNA is initially cloned in long sequences, e.g., 35-45 kilobases in cosmids, or like vector. After amplification the inserts are cut into smaller fragments and labeled for formation to a heterogeneous mixture. In this embodiment, the chromosomal binding sites of the fragments are clustered in the chromosomal regions complementary to the cloned "parent" nucleic acid sequence. Fluorescent signals from such clusters are more readily detected than signals from an equivalent amount of label dispersed over the entire chromosome. In this embodiment, the clusters are substantially uniformly distributed over the chromosome. (Page 13, line 23 - page 14, line 11).

The application thus teaches the use of one or more cosmids, each having a complexity of about 35-45 kb. This application thus sufficiently describes a labeled nucleic acid probe "having a complexity greater than about 40 kb," as now claimed.

Moreover, the Examples in the present specification employ labeled probes having a complexity of at least 40 kb as now claimed. Example V, for example, describes probes having 100 clones, each of 3 kb. *See*, for example, page 34, line 24 to page 38, line 12.

Still further, original claim 5, for example, recites that "labeled nucleic acid fragments are derived from substantially equal amounts of between about 10-1000 distinct cloned inserts each having a length within the range of between about 20-45 kilobases."

Similarly, support for claim 97, which recites that the complexity of the probe is greater than about 200 kb, is found in the '314 application. As previously stated, original claim 5, for example, recites that "labeled nucleic acid fragments are derived from substantially equal amounts of between about 10-1000 distinct cloned inserts each having a length within the range of between about 20-45 kilobases." Taking the lower limit of each range, the lower limit of the claimed complexity is obtained, *i.e.,* 10 distinct cloned inserts each having a length of about 20 provides a probe complexity of 200 kb. Complexities of greater than about 200 kb are obtained using the remainder of the disclosed ranges.

Because of the '314 application's description, including the example and claims, the '314 application provides written description for the now claimed subject matter. As stated by the Court in *In re Wertheim*, 191 USPQ 90, 98 (CCPA 1976):

> In the context of *this* invention, in light of the description of the invention as employing solids contents within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the Swiss disclosure so to conclude.

Moreover, as found acceptable by the Court in *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977), applicants here are claiming a subgenus (greater than about 40 kb) of a genus (greater than about 35 kb) fully disclosed and exemplified in the '314 application. As such, the written description requirement is met and applicants are entitled to priority of the '314 application.

In view of the above, Lichter et al. is not prior art to applicants. The rejection of the claims under §103(a) as purportedly obvious over Weissman et al . in view of Lichter et al. is thus improper and should be withdrawn.

However, even assuming *arguendo* that the Lichter et al. publication were prior art to the present Application, Applicants maintain that the present claims are not *prima facie* obvious over Weissman et al. in view of Lichter et al. The requirements of a *prima facie* case of obviousness are set forth in MPEP 2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Examiner asserts, at page 7 of the Official Action mailed September 22, 1999 (Paper No. 52), that Weissman et al. disclose

> in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to disease. Probed regions are disclosed as 50 kb to 200 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as instantly claimed.

However, Applicants respectfully maintain that Weissman et al. does not discuss probe complexity at all. The passage pointed to by the Examiner refers to the length of probed (*i.e.*, target) regions to be stained, not to probe complexity.

Weissman *et al.* describes the detection of chromosomal rearrangements, *e.g.*, the spacing between genes including linkage that may be related to a disease. Weissman,

however, fails to disclose or even suggest applicants' invention as now claimed. Weissman is unrelated to a method of staining targeted chromosomal material based upon nucleic acid segment employing high complexity nucleic acid probes of greater than 40 kb together with blocking nucleic acid and/or removal of repeats, in in situ hybridization, as claimed by applicants. Weissman is further unrelated to a method wherein the chromosomal DNA stained "is present in a morphologically identifiable chromosome or cell nucleus during the in situ hybridization," as recited in the claims. Nor does Weissman provide any motivation to stain targeted chromosomal material using such high complexity nucleic acid probes and blocking nucleic acid or removal of repeats in a method as claimed.

Lichter et al. does not remedy the deficiencies of Weissman et al. First, Lichter et al. begin with a probe set containing 94 kb of insert DNA (p. 9664, last paragraph of col. 2). Lichter et al. do not explicitly define this measurement as either length or complexity. However, Lichter et al. go on to state that "the probe concentration was decreased in proportion to the sequence complexity of the probe mixture." (sentence bridging pp 9664-9665), and conclude by pointing out that "when probe sets containing 29 kb or less of target sequence were used, the fluorescein isothiocyanate detection was generally enhanced by one cycle of signal amplification." (p. 9664, third paragraph in col 1). Thus, while Lichter et al does not explicitly address the complexity of their probe set, even if the 94 kb and 29 kb are assumed to refer to complexity, Lichter's assertion that use of 29 kb is advantageous teaches away from the use of probes of about 40 kb of complexity, about 50 kb, or greater, as recited in the instant claims.

> When prior art references require a selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. Something in the prior art as a whole must suggest the desirability, and thus the obviousness of making the combination.

Uniroyal, Inc. v. Rudkin-Wiley Corp., 5 USPQ2d 1434 (Fed. Cir. 1988). Not only are all of the limitations of the present claims neither taught nor suggested by the cited publications, but also the cited art does not suggest the desirability of modifying the disclosures thereof in order to arrive at the present invention. Accordingly, the presently claimed invention is not *prima facie* obvious over Weissman et al. in view of Lichter et al. Withdrawal of this rejection is thus respectfully requested.

3. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claim 125 of copending application Serial No. 08/473,327.

While Applicants do not concede that the present claims are obvious over claim 125 of copending application Serial No. 08/473,327, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

4. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 1, 48, and 50-58 of copending application Serial No. 08/477,316.

While Applicants do not concede that the present claims are obvious over claims 1, 48, and 50-58 of copending application Serial No. 08/477,316, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

5. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 1 and 48 of copending application Serial No. 08/487,387.

While Applicants do not concede that the present claims are obvious over claims 1 and 48 of copending application Serial No. 08/487,387, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

6. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 62-65 and 125-148 of copending application Serial No. 08/478,740.

While Applicants do not concede that the present claims are obvious over claims 62-65 and 125-148 of copending application Serial No. 08/478,740, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

7. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 18-33 of copending application Serial No. 08/472,312.

While Applicants do not concede that the present claims are obvious over claims 18-33 of copending application Serial No. 08/472,312, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

8. The provisional rejection of Claims 72, 74, 76-86, 88-93, 95-97, and 102-104 under the judicially-created doctrine of obviousness-type double patenting as purportedly obvious over claims 131, 132, 144-147, and 150-153 of copending application Serial No. 08/487,974.

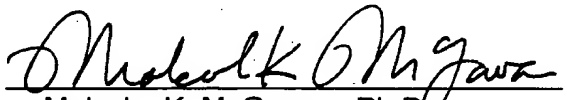
While Applicants do not concede that the present claims are obvious over claims 131, 132, 144-147, and 150-153 of copending application Serial No. 08/487,974, Applicants hereby express a willingness to consider filing a Terminal Disclaimer in either case upon an indication that the claims in both cases are otherwise allowable.

IX. Conclusion

For the foregoing reasons, Applicants respectfully request the withdrawal of the rejections of the present claims, and an indication that the claims are allowable.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 
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APPENDIX

The Appealed Claims

48. A method of staining target chromosomal material comprising:

(a) providing at least one labeled nucleic acid probe having a complexity greater than about 40 kb, which labeled nucleic acid probe comprises fragments which are substantially complementary to unique nucleic acid segments within the chromosomal material for which detection is desired, and providing blocking nucleic acid that comprises fragments which are substantially complementary to repetitive segments in the labeled nucleic acid; and

(b) employing said labeled nucleic acid probe, blocking nucleic acid, and chromosomal DNA in in situ hybridization so that labeled repetitive segments, if present, are substantially blocked from binding to the chromosomal DNA, while hybridization of unique segments within the labeled nucleic acid probe to the chromosomal DNA is allowed, wherein blocking of the labeled repetitive segments is sufficient to permit detection of hybridized labeled nucleic acid containing unique segments, and wherein the chromosomal DNA is present in a morphologically identifiable chromosome or cell nucleus during the in situ hybridization.

49. The method of claim 48, wherein the chromosomal DNA is present in a morphologically identifiable chromosome.

50. The method of claim 48, wherein the chromosomal DNA is present in a cell nucleus during the in situ hybridization.

51. The method of claim 48, wherein the chromosomal material is from a fetal cell.

52. The method of claim 49, further comprising the step of separating the fetal cell from maternal blood.

53. The method of claim 48, wherein the labeled nucleic acid probe comprises heterogeneous mixtures of labeled nucleic acid fragments, wherein the nucleic acid fragments are substantially complementary to sites on the targeted chromosomal material and are substantially free of nucleic acid sequences having a hybridization capacity to sites on chromosomal material that is not targeted.

54. The method of claim 48, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of extra or missing chromosomes.

55. The method of claim 48, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of extra or missing portions of a chromosome.

56. The method of claim 48, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of chromosomal rearrangement.

57. The method of claim 56, wherein the chromosomal rearrangement is an inversion.

58. The method of claim 56, wherein the chromosomal rearrangement is an insertion.

59. The method of claim 56, wherein the chromosomal rearrangement is a translocation.

60. The method of claim 56, wherein the chromosomal rearrangement is an amplification.

61. The method of claim 56, wherein the chromosomal rearrangement is a deletion.

62. The method of claim 48, wherein the target chromosomal material is present in an interphase cell nucleus.

63. The method of claim 62, wherein the labeled nucleic acid has a complexity of between about 40 kb and 100 kb.

64. The method of claim 62, wherein the labeled nucleic acid has a complexity between about 50 kb and 400 kb.
(This claim is objected to, but would be allowable if independent.)

65. The method of claim 48, wherein the labeled nucleic acid comprises fragments complementary to the total genomic complement of chromosomes.

66. The method of claim 48, wherein the labeled nucleic acid comprises fragments complementary to a single chromosome.

67. The method of claim 48, wherein the labeled nucleic acid comprises fragments complementary to a subset of chromosomes.

68. The method of claim 48, wherein the labeled nucleic acid comprises fragments complementary to a subregion of a single chromosome.

69. The method of claim 48, wherein the labeled nucleic acid is designed to allow detection of cancer.

71. The method of claim 48, further comprising removing from the labeled nucleic acid fragments which are substantially complementary to repetitive segments within the target chromosomal material.

72. (Amended) A method of staining target interphase chromosomal DNA comprising:
(a) providing at least one labeled nucleic acid probe having a complexity greater than about 40 kb which labeled nucleic acid probe comprises fragments which are substantially complementary to unique nucleic acid segments within the chromosomal DNA for which detection is desired, wherein the nucleic acid probe is substantially free of repetitive segments which are complementary to repetitive segments in the target interphase chromosomal material; and
(b) employing said labeled nucleic acid probe and chromosomal DNA in in situ hybridization so that hybridization of unique segments within the labeled nucleic acid probe to the chromosomal DNA is allowed, and hybridized labeled nucleic acid containing unique segments are detected, and wherein the interphase chromosomal DNA is present in a morphologically identifiable cell nucleus during the in situ hybridization.

73. The method of claim 72, further comprising providing blocking nucleic acid that

comprises fragments which are substantially complementary to repetitive segments in the labeled nucleic acid probe and employing said blocking nucleic acid in in situ hybridization so that labeled repetitive segments, if present, are substantially blocked from binding to the chromosomal DNA.

74. The method of claim 72, wherein the chromosomal DNA is present in a morphologically identifiable chromosome.

75. The method of claim 72, wherein the chromosomal DNA is present in a cell nucleus during the in situ hybridization.

76. The method of claim 72, wherein the chromosomal material is from a fetal cell.

77. The method of claim 76, further comprising the step of separating the fetal cell from maternal blood.

78. The method of claim 72, wherein the labeled nucleic acid probe comprises heterogeneous mixtures of labeled nucleic acid fragments, wherein the nucleic acid fragments are substantially complementary to sites on the targeted chromosomal material and are substantially free of nucleic acid sequences having a hybridization capacity to sites on chromosomal material that is not targeted.

79. The method of claim 72, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of extra or missing chromosomes.

80. The method of claim 72, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of extra or missing portions of a chromosome.

81. The method of claim 72, wherein the labeled nucleic acid probe comprises fragments which are designed to allow detection of chromosomal rearrangement.

82. The method of claim 81, wherein the chromosomal rearrangement is an inversion.

83. The method of claim 81, wherein the chromosomal rearrangement is an insertion.

84. The method of claim 81, wherein the chromosomal rearrangement is a translocation.

85. The method of claim 81, wherein the chromosomal rearrangement is an amplification.

86. The method of claim 81, wherein the chromosomal rearrangement is a deletion.

88. The method of claim 87, wherein the labeled nucleic acid has a complexity of between about 40 kb and 100 kb.

89. The method of claim 87, wherein the labeled nucleic acid has a complexity between about 50 kb and 100 kb.

90. The method of claim 72, wherein the labeled nucleic acid comprises fragments complementary to the total genomic complement of chromosomes.

91. The method of claim 72, wherein the labeled nucleic acid comprises fragments complementary to a single chromosome.

92. The method of claim 72, wherein the labeled nucleic acid comprises fragments complementary to a subregion of a single chromosome.

93. The method of claim 72, wherein the labeled nucleic acid is designed to allow detection of cancer.

95. The method of claim 72, wherein the targeted chromosomal material is a genetic rearrangement associated with chromosome 21 in humans.

96. (Amended) The method of claim 72, wherein fragments substantially complementary to repetitive segments in the target interphase chromosomal material are removed from the labeled nucleic acid probe.

97. The method of claim 72, wherein the complexity of the labeled nucleic acid probe is greater than about 200 kb.

Allowed claims:

98. A method of staining target chromosomal material comprising:

(a) providing at least one labeled nucleic acid probe having a complexity greater than about 50 kb, which labeled nucleic acid probe comprises fragments which are substantially complementary to unique nucleic acid segments within the chromosomal material for which detection is desired, and providing blocking nucleic acid that comprises fragments which are substantially complementary to repetitive segments in the labeled nucleic acid; and

(b) employing said labeled nucleic acid probe, blocking nucleic acid, and chromosomal DNA in *in situ* hybridization so that labeled repetitive segments, if present, are substantially blocked from binding to the chromosomal DNA, while hybridization of unique segments within the labeled nucleic acid probe to the chromosomal DNA is allowed, wherein blocking of the labeled repetitive segments is sufficient to permit detection of hybridized labeled nucleic acid containing unique segments, and wherein the chromosomal DNA is present in a morphologically identifiable chromosome or cell nucleus during the *in situ* hybridization.

99. The method of claim 98, wherein the target chromosomal material is present in an interphase cell nucleus.

100. The method of claim 99, wherein the labeled nucleic acid has a complexity of between about 50 kb and 400 kb.

101. The method of claim 100, wherein the labeled nucleic acid has a complexity between about 50 kb and 100 kb.

102. A method of staining target interphase chromosomal DNA comprising:

(a) providing at least one labeled nucleic acid probe having a complexity greater than about 50 kb which labeled nucleic acid probe comprises fragments which are substantially complementary to unique nucleic acid segments within the chromosomal DNA for which detection is desired, wherein the nucleic acid probe is substantially free of repetitive segments which are complementary to repetitive segments in the target interphase chromosomal material; and

(b) employing said labeled nucleic acid probe and chromosomal DNA in *in situ* hybridization so that hybridization of unique segments within the labeled nucleic acid probe to the chromosomal DNA is allowed, and hybridized labeled nucleic acid containing unique segments are detected, and wherein the interphase chromosomal DNA is present in a morphologically identifiable cell nucleus during the *in situ* hybridization.

103. The method of claim 102, wherein the labeled nucleic acid has a complexity of between about 50 kb and 400 kb.

104. The method of claim 103, wherein the labeled nucleic acid has a complexity between about 50 kb and 100 kb.